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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/561,097

12/16/2005

Matthew Baker

MER-141

9422

2387 7590 07/16/2008

Olson & Cepuritis, LTD.  
20 NORTH WACKER DRIVE  
36TH FLOOR  
CHICAGO, IL 60606

EXAMINER

SPECTOR, LORRAINE

ART UNIT

PAPER NUMBER

1647

MAIL DATE

DELIVERY MODE

07/16/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/561,097	<b>Applicant(s)</b> BAKER ET AL.	
	<b>Examiner</b> Lorraine Spector, Ph.D.	<b>Art Unit</b> 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 May 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 16-34 is/are pending in the application.
- 4a) Of the above claim(s) 32 and 33 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 34 is/are allowed.
- 6) ☒ Claim(s) 16-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 16-34 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 December 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election without traverse of SEQ ID NO: 6 in the reply filed on 5/8/2008 is acknowledged.

Applicants did not specifically point out which claims correspond to the elected invention. The Examiner believes that claims 16-31 and 34 correspond to the elected invention. In the interest of compact prosecution, those claims will be examined.

Claims 32- 33 are withdrawn from prosecution as being drawn to non-elected inventions.

### ***Claim Objections***

Claims 16-32 are objected to for reading on non-elected species. Correction is required. There is no generic claim, and hence allowability of a generic claim cannot occur.

### ***Specification***

The disclosure is objected to because of the following informalities:

The brief description of figure 12 indicates hatched bars, whereas the bars on the figure are not hatches.

The specification is objected to for including as tables amino acid sequences. There is no need for such, as the sequence listing will be printed as part of the patent. Further, the material is not tabular in nature, and finally, listing the sequences in that fashion invites printer error.

Applicants are advised to delete "tables" that are merely sequences, and further, to renumber all subsequent tables, including all references to such in the specification.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 20, 21, 22, 25, 27, 29, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 34 is indefinite because it is not clear whether “defined” means “consisting”, “comprising”, or allows some level of alteration.

Claims 18, 20, 21, 22, 25, 27 and 29 are indefinite because the term “having” has no set meaning as it relates to patent law. It is not clear whether it is intended to mean "consisting", comprising', or some other meaning. Accordingly, it is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein of SEQ ID NO:6 or proteins having mutations L69A and G73A (in view of Park et al., see below) and fusion proteins comprising such, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of

direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn broadly to muteins of TPO, Wherein the protein comprises at least the first 163 amino acids (sufficient to confer biological activity as taught by Thomas, previously of record), and wherein up to 13 individual amino acids may be substituted. Because various residues may be substituted at particular positions, and because substitutions are not required at all positions, the number of species actually encompassed by the claims is large. It is noted that the substitutions in the elected species are not conservative substitutions.

It is noted that the specification discloses the invention as being a less-immunogenic form of TPO. However, this limitation is not reflected in the claims. It is also noted that although clone 37101 was shown to have 40% of the activity of wild-type TPO *in vitro*, and that no tests were done to determine whether the entire molecule was less immunogenic than the wild-type; only fragments of the molecule were tested for such. The protein is deemed to be useful *in vitro*, at the very least.

The prior art (Thomas, for instance) teaches making substitution mutants of TPO; see for example column 9, lines 19-33 and column 10, lines 33-63. Also known were chimeric molecules comprising TPO; col. 9, lines 34-40. See also claims 11-13; claim 13 is specifically drawn to TPO that is non-immunogenic in a human. Park et al, JBC 173(1):256-61, 1998, demonstrate that alanine substitutions at the positions applicants designate as X1 and X10 have no biological activity, further showing the unpredictability of making substitutions; see Table II, muteins E50A and E72A, both of which are claimed herein.

The working examples in the specification test the immunogenicity of small substituted peptides derived from TPO *in vitro*. Those peptides are not tested *in vivo*, and are not tested for immunogenicity as part of a longer, biologically active molecule, either *in vitro* or *in vivo*. A limited number of proteins are tested for activity *in vitro*, see Table 5. All had lower activity than wild-type hTPO. Even the elected species only had 40% activity as compared to wild-type.

Predictability in the art is low. The testing of small peptides absent the rest of the molecule is unpredictable, because it removes the effects of secondary and tertiary structure. It is not predictable which mutations would be exposed on the resultant protein in a fashion that

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would actually affect immunogenicity *in vivo* when presented as part of a longer, biologically active molecule. Further, such experiments would have to be conducted in humans, which, given the nature of TPO, is very dangerous, and constitutes undue experimentation in and of itself.

Thus, given that *no* species was tested *in vivo*, that only limited species were tested for activity when present as part of a protein long enough to have activity (table 5), that *no* fusion proteins were tested, that of the innumerable mutations only 10 individual fragments having mutations were tested for immunogenicity, but never *in vivo* nor as part of an active molecule (see Figure 3). The Examiner concludes that it would take undue experimentation to determine which of the innumerable species would be active and thus useful, and further that the specification does not enable the person of ordinary skill in the art to use those species that are not.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Park et al., JBC 173(1):256-61, 1998.

Park et al. made alanine substituted muteins of TPO, at positions corresponding to X1, X9, X11 and X12 of the claims; see Figure 1. At page 261, first column, they state that full-length molecules comprising those mutations were used in the biological activity assays. Accordingly, the claims are anticipated by Park et al.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 19, 21, 30 rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al., as cited above, in view of Gillies et al., U.S. Patent No. 7,186,804.

The teachings of Park et al. are summarized above. Park does not teach making an Ig fusion protein.

Gillies et al. teach making IgG4 fusion proteins for the purpose of prolonging serum half life of the protein fused thereto. See claim 11, which recites SEQ ID NO: 37, which is 97% identical to SEQ ID NO: 73 of the instant application.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Park et al. by making an IgG4 fusion protein in view of Gillies teaching that such is useful to extend serum half-life of a biologically active protein. It is noted that the fusion proteins would spontaneously dimerize, meeting the limitations of claims 30-31. Accordingly, the invention is *prima facie* obvious.

While there is 3% difference in the IgG4 sequence between Gillies et al. and SEQ ID NO: 73, the difference is considered to be *de minimus*, and not to constitute an inventive contribution. The specification does not address the difference in sequence between SEQ ID NO: 73 and the standard IgG4 of the prior art as exemplified by Gillies et al., nor does it allege any advantage or different property resulting from the differences.

The Examiner's position is supported by the case law. For example, see *Ex parte Anderson*, 30 USPQ2d 1866, 1993, which held that "Applicants have not explained practical advantages of differences in DNA structure between claimed sequence and prior art", and therefore that minor sequence differences with no net effect are not patentably distinct. See also *In re Best, Bolton, and Shaw*, 1958 USPQ 430, which held that the PTO can require applicant to prove that prior art products do not possess characteristics of the claimed product where the

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claimed product and prior art products are identical or substantially identical. The case stated that in such situations, the burden of proof is on the applicant. In this case, there are *de minimus* sequence differences between SEQ ID NO:73 and the prior art, but there are no practical advantages ascribed thereto.

Claims 18, 20, 22 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6238890.

The rejected claims add the limitation that SEQ ID NO: 5 is used as a linker.

SEQ ID NO: 5 (GSGSGSG) is a linker sequence commonly used in recombinant protein expression because of its well-known flexibility. A search of the issued patent database revealed no fewer than 377 100% hits on SEQ ID NO: 5, for example see Boime, U.S. Patent No. 6238890, SEQ ID NO: 52. While SEQ ID NO: 52 contains one additional "S" residue, the language of the claims, "having", is taken to be open language, allowing such as residue. Further, Boime et al. teach:

"Detailed Description Text - DETX (291):

"Linker" refers to a sequence containing repeating glycine and serine amino acids such as GS, GSGS (SEQ ID NO:80), GSGSGS (SEQ ID NO:81), GSGSGSGS (SEQ ID NO:52), GSGSGSGSGS (SEQ ID NO:82) or any other sequence of amino acids that permits the .beta.- and .alpha.-subunit sequences of the single chain gonadotropin to form a complex in which the .alpha.- and .beta.-subunit portions combine with the .beta.- and .alpha.-subunit portions of the same or other molecule."

Accordingly, It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use a linker such as SEQ ID NO: 5 to connect the TPO and Ig portions of the molecule in view of the art-recognized advantages thereof, especially the flexibility of the linker. Accordingly, the invention is *prima facie* obvious.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.



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Epitope mapping is notoriously old and well-known in the art, as is the use of such for the ultimate reduction of immunogenicity; see for example U.S. Patent Nos. 7101674 and 7122634. However, there is no prior art on doing so with thrombopoietin, nor are the specific mutations comprised in SEQ ID NO: 6 known in the art. Accordingly, claim 34 would be allowable if amended to overcome the rejection under 35 U.S.C. §112, second paragraph.

Claims 23-29 would be allowable if restricted to the elected subject matter, which would also overcome the rejection under 35 U.S.C. §112, first paragraph.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.  
Primary Examiner

Application/Control Number: 10/561,097  
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### Sequence Alignments

S-10-310-719-37

; Sequence 37, Application US/10310719

; Patent No. 7186804

; GENERAL INFORMATION:

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; APPLICANT: Gillies, Stephen
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; TITLE OF INVENTION: Immunocytokines With Modulated Selectivity

; FILE REFERENCE: LEX-020

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; CURRENT APPLICATION NUMBER: US/10/310,719
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; CURRENT FILING DATE: 2002-12-04
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; PRIOR APPLICATION NUMBER: 60/337,113

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; PRIOR FILING DATE: 2001-12-04

; PRIOR APPLICATION NUMBER: 60/371,966

; PRIOR FILING DATE: 2002-04-12

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; NUMBER OF SEQ ID NOS: 37
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; SOFTWARE: PatentIn version 3.1
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; SEQ ID NO 37

; LENGTH: 580

; TYPE: PRT

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; ORGANISM: Artificial Sequence
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; FEATURE:

; OTHER INFORMATION: dI-NHS76 (gamma4h) (FN>AQ)-ala-IL2 (D20T) heavy chain fused to

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; OTHER INFORMATION: IL-2 variant

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US-10-310-719-37

Query Match 97.2%; Score 1219; DB 3; Length 580;  
Best Local Similarity 97.0%; Pred. No. 1e-110;  
Matches 225; Conservative 2; Mismatches 5; Indels 0; Gaps 0;

[illegible]

Db 216 EPKSCDKTHTCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQF 275

Qy 61 NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT 120

Qy 121 ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP 180

Qy 181 PVLDS DGSFFLYSKLTVDKSRWQOGNIFSCSVMHEALHNHYTQKSLSLSPGA 232

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	5
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Db 396 PVLDS DGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNHYTQKSATATPGA 447

US-08-918-288-52

; Sequence 52, Application US/08918288

; Patent No. 6238890

; GENERAL INFORMATION:

; APPLICANT: BOIME, Irving

APPLICANT: MOYLE, William R.

TITLE OF INVENTION: SINGLE-CHAIN FORMS OF THE

; TITLE OF INVENTION: GLYCOPROTEIN HORMONE QUARTET

; NUMBER OF SEQUENCES: 83

CORRESPONDENCE ADDRESS:

Art Unit: 1647

```
;      ADDRESSEE:  MORRISON & FOERSTER
;      STREET:    2000 Pennsylvania Avenue, NW, suite 5500
;      CITY:     Washington
;      STATE:    DC
;      COUNTRY:  USA
;      ZIP:      20006-1888
;      COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Diskette
;      COMPUTER:  IBM Compatible
;      OPERATING SYSTEM:  DOS
;      SOFTWARE:  FastSEQ for Windows Version 2.0
;      CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/918,288
;      FILING DATE:
;      CLASSIFICATION:
;      PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  09/282,357
;      FILING DATE:
;      APPLICATION NUMBER:  08/853,524
;      FILING DATE:  09-MAY-1997
;      APPLICATION NUMBER:  08/199,382
;      FILING DATE:  18-FEB-1994
;      ATTORNEY/AGENT INFORMATION:
;      NAME:      Murashige, Kate H
;      REGISTRATION NUMBER:  29,959
;      REFERENCE/DOCKET NUMBER:  29500-20050.25
;      TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  202-887-1500
;      TELEFAX:   202-887-0763
;      TELEX:
;      INFORMATION FOR SEQ ID NO:  52:
;      SEQUENCE CHARACTERISTICS:
;      LENGTH:    8 amino acids
;      TYPE:      amino acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
US-08-918-288-52
```

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Query Match          100.0%;  Score 36;  DB 2;  Length 8;
Best Local Similarity 100.0%;  Pred. No. 9.5e+05;
Matches      7;  Conservative    0;  Mismatches    0;  Indels      0;  Gaps      0;
```

```
Qy      1 GSGSGSG 7
        |||||
Db      1 GSGSGSG 7
```